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The prescription of the vitamin D and biochemical tests in tumours of the female reproductive system

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The results of a study conducted to compare the diagnostic role of vitamin D, calcium and phosphorus in patients with various tumours in the female reproductive system have been presented in this article. For the research, 50 women diagnosed with a tumour in the reproductive system were selected. The concentrations of vitamin D, parathormone (PTH), calcium and phosphorus were determined in all patients by immunoenzyme and biochemical methods. The concentration of vitamin D in patients with a malignant tumour was 2.2 fold higher than that in patients with a benign tumour. Moreover, the concentrations of the calcium and phosphorus in patients with a malignant tumour were significantly lower in comparison with the control group, while the concentration of PTH increased. Thus, these markers can be used for early diagnosis and screening of female genital tumours.

Keywords: *Cancer of the female reproductive system, vitamin D, parathormone, calcium, phosphorus*

INTRODUCTION

Vitamin D deficiency is widespread worldwide global public health problem. Determination of the level of vitamin D used not only in studies that are about prolonging life but also in other studies that confirm the presence of the pathological process.

Vitamin D plays an important role in the protective function of the immune system. Vitamin D deficiency is a serious health problem, which increases the risk of many diseases, as well as the risk of cancer formation. Statistics show that the formation of cancer in the female reproductive system is rapidly increasing among women (Siegel et al., 2017). Recently, large-scale studies show the role of vitamin D in the pathogenesis of certain types of oncological diseases, such as colorectal and lung cancer. Studies show that there is a link between a decrease in vitamin D concentration and an increase in the incidence of female genital cancer. Researches show, that calcitriol and other forms of vitamin D have a proapoptotic, antiproliferative, and antimetastatic effect on cancer tissue by altering the expression of many transcription factors of apoptosis and proliferation (Кобякова и др., 2015).

Recent investigations on the metabolism and biological effects of vitamin D bring to a radical change in the known information about its role and importance in the body (Захарова и др., 2013).

The hormonal system of active metabolites of vitamin D stimulates the synthesis and resorption of bone tissue (Lappe et al., 2004). During the sufficient concentration of vitamin D in the body, the calcium absorption reaches 30% in the intestine and 60-80% during the active growth of the child. Deficiency of vitamin D leads to a reduction of calcium absorption. Low levels of ionized calcium stimulate the secretion of parathyroid hormone, which in turn accelerates the reabsorption of calcium in the kidneys and its absorption from the small intestine (Turti et al., 2017; Golden and Abrams, 2014). Increased levels of parathyroid hormone have an adverse effect on the amount of phosphate in the blood, as it slows renal reabsorption, increases the loss of phosphorus in the urine, and as a result, its level in the blood decreases. Decreased levels of phosphorus and calcium in the body cause changes in bone mineralization (Dobnig et al., 2008; Maltsev et al., 2008). An elevated level of the parathyroid hormone considered an

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early and very reliable indicator of vitamin D deficiency (Rastogi et al., 2013).

It should be noted that this hormone maintains the concertation of the calcium in the body and together with vitamin D metabolites the constant stabilization in the organism achieves. The study of phosphorus-calcium metabolism is not enough to assess the condition of vitamin D in the body, since the level of total calcium in the organism is stable. During Vitamin D deficiency and decreased intestinal absorption of calcium, bone resorption maintained for a long time, due to the parathyroid hormone.

In these studies, the effect of vitamin D and vitamin D receptors on endometrial, ovarian, cervical, vulvar, and vaginal cancers analyzed systematically.

Environmental studies show a positive correlation between vitamin D synthesis and decrease the risk for ovarian cancer (Gagel, 2006).

Vulvar cancer is the most common gynecological cancer, accounts for 3% to 5% of all genital cancer cases in women (Parkin et al., 2015). Taking into account the lymph node metastases among these patients, the recovery rate for five-year is 40% (Beller et al., 2006). Vitamin D receptor found in the non-pathological ovarian epithelium, as well as in ovarian tumours. It is important for ovarian function and affects the biosynthesis of estrogen receptors (Lurie et al., 2007). Vaginal carcinoma is a rare gynecological malignancy, accounts for only 1-2% (Parkin et al., 2015).

Preclinical and epidemiological evidence shows that the presence of vitamin D in the body reduces the risk of gynecological cancer [Holick, 2007; Walentowicz-Sadlecka et al., 2013).

Studies that investigate the effect of vitamin D and its receptor on tumour formation in the female reproductive system are few.

Studies show that women with a high level of vitamin D have a lower risk (15 to 25%) of the breast, colon, endometrial and rectal cancer. High level of vitamin D can increase the chances of surviving even after cancer diagnosticate (Reichrath et al., 1998). The metabolism of vitamin D in the body is closely linked with the levels of calcium, phosphorus and magnesium, as well as parathyroid hormone (PTH). PTH plays an important role in calcium-phosphorus metabolism by regulating the stable concentration of calcium and phosphorus in the extracellular fluid. Study of recent decades show that vitamin D deficiency may alter calcium-phosphorus metabolism and thus can lead to a number of degenerative changes in bone formation (Holick, 2007).

Vitamin D deficiency is now seen as a common problem in women and thus, there is a need to increase its level.

The aim of the study was to investigate vitamin D deficiency as well as calcium-phosphorus metabolism in women with various genital cancers.

MATERIALS AND METHODS

The fresh blood samples collected on a voluntary basis from 50 women diagnosed with genital cancer who had applied to the Oncology Clinic of the Azerbaijan Medical University and received treatment. The studied include 28 women diagnosed with uterine cancer, 25 with cervical cancer, and 7 with vulvar cancer. The diagnosis confirmed based on general instrumental examination methods and pathohistological opinion. The control group consisted of 20 healthy individuals.

Blood samples from case and control group taken to determine the concentration of vitamin D, calcium, PTH and phosphorus from the blood serum.

The concentration of vitamin D in blood serum was determined by immunoenzyme analysis with the reagent kit belonging to the company "Bioaktiva Diganostica". The concentration of calcium and phosphorus was analyzed by colorimetric method using "Human" kit.

Statistical analysis of the obtained results was calculated by the Student non-parametric method.

RESULTS AND DISSCUSION

The metabolic activity of vitamin D, regardless of the source of the vitamin (exogenous or endogenous) or its chemical form (cholecalciferol or ergocalciferol), achieved through a number of enzymatic pathways that differ from each other. Vitamin D enters the body through food (dairy products, eggs, fish and meat). In addition, under the influence of ultraviolet rays, vitamin D is synthesized from 7-hydroxy-cholesterol in the skin and

provides 90-95% of the body's need for vitamin D. Meanwhile, provitamin D undergoes enzymatic transformations in the liver and kidneys and converted into the active metabolite 1,25-dihydroxivitamin D3 (1,25 (OH)-D3). 25(OH)-D3 is stored in adipose tissue and is an accurate biomarker of the body's overall vitamin D status. Two major metabolites formed during the metabolism of 25(OH)-D3: 24.25-dihydroxycholecalciferol [24.25(OH)2-D3] or 25-dihydroxycholecalciferol [1.25(OH)2-D3] (Dobnig et al., 2008). The level of 25(OH)-D3 determined in the study.

The results show that concentration of vitamin D in control group varies from 11.5-39.8 nq/ml and in average reached to 25.82±0.29 ng/ml. In female genital cancer, the level of vitamin D varies between 5.80-24.60 ng/ml and in average reached to 11.51±0.18 ng/ml. According to statistics, level of vitamin D decrease in 2.2-fold (p<0.001) in patients with genital cancer (Figure).

Low levels of vitamin D caused by liver or kidney disease, taking certain medications, limited epidermal synthesis of cholecalciferol (living in low-radiation areas, low exposure to sunlight, etc.). Vitamin D and calcium metabolism is an important factor for bone health (Maltsev et al., 2012). The study showed that the concentration of PTH in female genital cancer increased by 32% (p<0.01) compared to the control group and in average reached to 29.6±0.5 pg/ml. The concentration of this hormone varies in the range of 14.8-48.9 pg/ml. Meanwhile, the concentration of PTH in the control group varies in the range of 13.5-24.6 pg/ml, and the average is 22.4±2.8 pg/ml. It is known that there is an inverse relationship between the secretion of PTH and the concetration of calcium in the blood. So, when calcium ions in the blood decrease, the secretion of the hormone increases. Vitamin D is an active regulator of calcium-phosphorus metabolism in the body. PTH maintains normal calcium levels in the blood, especially ionized calcium, by affecting the intestinal absorption function of calcium through the activated form of vitamin D (calcitriol) (Rastogi et al., 2013).

Vitamin D deficiency leads to serious disorders in calcium-phosphorus metabolism. Thus, vitamin D deficiency slows down the absorption of calcium from the intestine and disrupts the calcium-phosphorus metabolism in the body.

Significant change in concentration of potassium and phosphorus observed in the blood of patients with tumours in female reproductive system. Thus, the concentration of calcium in the blood serum of these patients is significantly reduced (22.9%) compared to the control group (p<0.01). The concentration of calcium in patients with cancer of the female reproductive organs is 7.98±0.16 mg/dl (control: 9.81± 0.16 mg/dl).

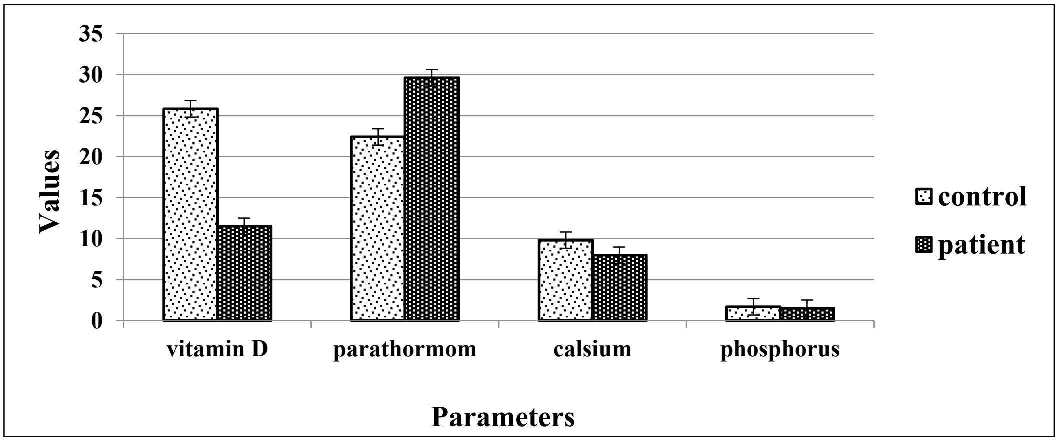


Fig. 1. Alteration of concentration of vitamin D and parathyroid hormone as well as calcium-phosphorus metabolism in patients with malignant tumors of the female reproductive system.

Table 1. Results of vitamin D, PTH and calcium-phosphorus metabolism in tumors of the female reproductive system

Groups	Results			
	Vitamin D3, nq/ml	Parathormon, pq/ml	Calcium, mq/dl	Phosphorus, mq/ml
Female patient with tumour in reproductive system (n=50)	11.51±0.18*** (5.80-24.00)	29.60±050 (14.80-48.90)**	7.98±0.16** (7.15±0.80)	1.52±0.26* (1.89-2.34)
Control (n=20)	25.82±0.29 (5.80-24.60)	22.40±2.80 (13.50-24.60)	9.81±0.16 (8.75-10.96)	1.69±0.35 (1.54-1,75)

Note: ***- p<0.001; ** - p<0.01, *** - p<0.001.

Deficiency of vitamin D also leads to a decrease in concentration of phosphorus. The concentration of phosphorus in the blood serum of patients is 1.52±0.26 mg/dl (1.69±0.35). According to the results of the comparative analysis, concentration of phosphorus decreases by 11.2% (p<0.005) compared to the control.

Based on the age, sex, and hormonal status the calcium intake prescribed as a protective method against decrease of calcium concentration in the body (Beller et al., 2006). In addition, the intake of vitamin D can increase the concentration of phosphorus in the body. Thus, the results show that vitamin D and its receptor play an important role in cancer of female reproductive system. In addition, vitamin D deficiency considered as a risk factor for cancer of the female reproductive system.

It is impossible to compensate for the physiological needs for vitamin D3 via food, therefore, its main source is the B-ultraviolet rays of the sun. Thus, these rays stimulate the synthesis of D3 from provitamin D (7-dehydrocholesterol) in the skin epidermis. This form of vitamin D regulates many physiological processes such as proliferation and differentiation of the epidermis. There are specific receptors for D3 (1.25(OH)2D that located in cells of various organs and tissues, including mitochondria. By possessing endocrine function, vitamin D regulates gene transcription in nearly 40 cells. Thus, vitamin D affects the transcription of the important genes which make 3% of the human genome and responsible for the synthesis of sex hormones and carbohydrate metabolism.

1.25 (OH) 2D is a biologically active form of vitamin D that binds to receptors located in the cell nucleus, activates the expression of specific genes in tissues, inhibits cell proliferation, induces apoptosis and differentiation, and prevents angiogenesis in cancer seeds. Experimental studies show that high doses of vitamin D suppress proliferation of epithelium and carcinogenesis. Vitamin D is involved in the process of carcinogenesis through two biological forms: $1.25(OH)_2D$ and 25(OH)D. 25 (OH) D enters cancer tissue and shows a certain anti-cancer effect. Later 1-α-hydroxylase promote the conversion of 25 (OH) D to 1, 25 (OH) and this conversion regulates cell proliferation, differentiation, and apoptosis. Calcium thought to have an anti-cancer effect in the presence of vitamin D, as calcium is one of the main mediators of vitamin D-induced apoptosis in cancer cells.

There is a metabolic relationship between Vitamin D and calcium, under normal physiological conditions. Calcium homeostasis plays an important role in the circulation of $1.25\ (OH)_2D$. Its level is inverse to the consumption of calcium. Reduction of the synthesis of $1.25\ (OH)\ _2D$ in response to a deficiency of trace element leads to a decrease in calcium absorption. In addition, $1.25\ (OH)_2D$ accelerates the release of calcium from cells into the bloodstream. On the other hand, the level of calcium in the blood affects the activity of 1-α-hydroxylase in the kidneys thereby increase the concentration of vitamin D.

Thus, vitamin D has a mechanism that differs from other classic vitamins and as a metabolic hormone has anti-proliferative, anti-apoptotic and anti-neongeon effects. The anti-cancer mechanisms of this vitamin in carcinogenesis not fully studied. The results show that maintaining optimal levels of vitamin 25 (OH)D in the blood is one of the most effective methods in the prevention of oncological diseases, including cancer of the female genital organs.

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Qadın cinsiyyət sisteminin şişləri zamanı vitamin D və biokimyəvi müayinələrin təyini

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Məqalədə qadın cinsiyyət sisteminin müxtəlif şişləri olan xəstələrdə vitamin D-nin, kalsium və fosforun diaqnostik rolunun müqayisəli öyrənilməsi məqsədilə aparılmış tədqiqat işinin nəticələri təqdim edilibdir. 50 qadın cinsiyyət sisteminin müxtəlif şişləri diqanozu qoyulmuş xəstə tədqiq edilibdir. Bütün xəstələrdə vitamin D-nin, parathormon (PTH), kalsium və fosforun qatılığı immunoferment və biokimyəvi metodlarla

təyin edilibdir. Bədxassəli şişlər olan xəstələrdə vitamin D-nin qatılığının xoşxassəli şişlər olan xəstələrlə müqayisədə 2,2 dəfə etibarlı artması müəyyən edilibdir. Bundan əlavə, bədxassəli şişlər olan xəstələrdə kalsium və fosforun qatılığının kontrola nsibətən əhəmiyyətli dərəcədə azalması, PTH-nun qatılığının isə əksinə artması aşkar edilibdir. Beləliklə, göstərilən bu markerlər qadın cinsiyyət orqanlarının şişlərinin erkən diaqnostikası və skrininqi üçün istifadə edilə bilər.

Açar sözlər: *Qadın cinsiyyət orqanlarının xərçəngi, vitamin D, parathormon, kalsium, fosfor*

Определение витамина D и биохимические исследования при опухолях женских половых органов

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В статье представлены результаты сравнительного исследования диагностической роли витамина D, кальция и фосфора у пациентов с различными опухолями женской репродуктивной системы. Исследовано 50 пациенток с различными опухолями женских половых органов. У всех больных концентрация витамин D, паратгормона (ПРГ), кальция и фосфора в сыворотке крови была определена иммуноферментным и биохимических методами. Установлено, что концентрация витамина D у пациентов со злокачественными опухолями по сравнению с пациентами с доброкачественными опухолями была достоверно выше в 2,2 раза. Также выявлено значительное уменьшение содержания кальция и фосфора, а также увеличение ПТГ у больных со злокачественными опухолями по отношению контролю. Таким образом, все эти маркеры могут быть использованы для ранней диагностики и скрининга при опухолях женских половых органов.

Ключевые слова: *Опухоль женских половых органов, витамин D, паратгармон, кальций и фосфор*